Remarks

A supplemental amendment was filed on August 30, 2007 along with an information disclosure statement filed on the same date. Apparently the supplemental amendment crossed in the mail with the present Office Action. Applicants request that the Examiner enter and consider the supplemental amendment in addition to the present response. Please note that the current listing of claims indicates the status of claims amended in the supplemental amendment as "previously presented."

The pending claims are 1-2, 8, 11, 15-16, 18-19, 21-35, 37, 42-43, 45-47, 50, 52-54, 56, 60, 62, 68, 70, 76-77, and 83-91. Claims 8, 11, 15-16, 18-19, 21, 23, 26-34, 37, 42, 53, 83, and 90 have been withdrawn from consideration. ***In the Office Action, claim 90 has been indicated as being withdrawn from consideration. This is incorrect, since claim 90 depends from claim 1, both of which read on the elected species. Cf. Applicants' response to Office Action mailed April 13, 2007, p. 52, and supplemental amendment, p. 52. Examiner is respectfully requested to consider claim 90 as previously presented and not withdrawn, and consequently under examination.***

The Examiner incorrectly states that claims 8, 11, 15-16, 18-19, 21, 23, 26-34, 37, 42, 53, 83, and 90 were withdrawn as being drawn to a non-elected *invention*. Only claims 37, 42, and 53 are directed to a non-elected *invention*. Claims 8, 11, 15-16, 18-19, 21, 23, 26-34, and 83 only fail to read on the elected *species*. These claims are subject to rejoinder when the patentability of an allowable generic claim that encompasses the elected species is established. As discussed above, claim 90 does indeed read on the elected species and should be considered for present examination.

Claims 54, 56, 60, 86, and 87-89 have been objected to under 37 CFR §1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 43, 45-47, 50, 52, 54, 56, 60, 62, 68, 70, 76-77, and 84-89 have been rejected under 35 U.S.C. §112 (1st paragraph) as failing to comply with the enablement requirement. Claims 1-2,

22, 35, and 91 have been rejected under 35 U.S.C. §103(a) as unpatentable over Yamamori, *et al.*, JP 2001-139550 ("Yamamori"). Claims 24 and 25 have been rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 5,705,521 to Abraham, *et al.* ("Abraham").

Restriction Requirement

The maintenance of the restriction requirement is acknowledged. Further reconsideration is respectfully requested. The Examiner acknowledges failure to follow PCT and WIPO guidelines in making the restriction requirement, but states that U.S. practice differs from PCT practice.

Applicants respectfully point out that the Examiner's statement as to the applicable law is incorrect. MPEP 1893.03(d) states:

> Examiners are reminded that unity of invention (not restriction) practice is applicable in international applications (both Chapter I and II) and in national stage application submitted under 35 U.S.C. §371.

This guideline clearly indicates that the unity of invention standards applied in §371 should be the same as those applicable to international preliminary examination (to which the WIPO guidelines directly apply). Applicants also cite to the decision of the Technology Center Director in a petition decision (of August 17, 2007) in application no. 10/506,005 where the Director found that claims to antibody conjugates of a compound should have been included with claims to the compound.

Applicants continue to be of the view that, for the reasons previously presented, the Examiner should find unity of invention as to Groups I, II and III and therefore that the restriction requirement should be withdrawn. Applicants are also of the view that the claims to antibody conjugates should be examined with claims to the corresponding compounds. Applicants therefore fully reserve the right to petition the restriction requirement.

Explanation of the Amendments

Claim 46 is amended merely to correct a clerical error, namely, to properly depend from claim 43, in order to establish proper antecedent basis.

Claims 54, 56, 60, 62, 68, and 76 are amended by deletion of the terms "radioprotective" and "cytoprotective," as appropriate, in order to establish proper antecedent basis.

Claim 90 is ***not*** withdrawn and the status so indicates. Please see discussion above.

Response to the Objections and Rejections

(1) Objection to Claims 54, 56, 60, and 86-89 under 37 CFR §1.75(c).

The Examiner has rejected claims 54, 56, 60, 86, and 87-89 under 37 CFR §1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 54, 56, 60 have been amended by deleting the terms "radioprotective" and "cytoprotective." In addition, claims 62, 68, and 76 have been amended by deleting the same aforementioned terms, as appropriate. Amended claims 54, 56, 60, 62, 68, and 76 are in proper dependent format, depending ultimately from claim 1, as required by the Examiner. Applicants believe that the scope of the claims as amended remains unchanged, and further, that due to these amendments, Applicants have not given up anything in terms of claim scope. In this regard, the specification fully describes the radioprotective and cytoprotective characteristics of the compound embodiments of the present invention. However, claims 86-89 do not depend from claim 1, as alleged in the Office Action. Rather, the claimed "radioprotective" compound of claims 86-87 and the claimed "cytoprotective" compound of claims 88-89 are clearly described by Formula I[ii]. Applicants respectfully traverse the objection to claims 86-89 and ask that it be withdrawn.

(2) Rejection of Claims 43, 45-47, 50, 52, 54, 56, 60, 62, 68, 70, 76-77, and 84-89 under 35 U.S.C. §112 (1st paragraph) enablement requirement.

The Examiner has maintained the rejection of claims 43, 45-47, 50, 52, 54, 56, 60, 62, 68, 70, 76-77, and 84-89, and further rejected claim 60 under 35 U.S.C. §112 as allegedly containing subject matter which is not described in the specification in such a way as to enable a person skilled in the art to make and/or use the invention. Applicants again respectfully traverse the rejection.

The Examiner states that he "disagrees" with Applicants' statement that Applicants enjoy a presumption that the claims comply with the enablement requirement of 35 U.S.C. § 112. Although the Examiner might disagree with the wisdom of the numerous court decisions setting forth the standard, the Examiner may be assured that Applicants accurately stated the applicable law, which is binding on the Examiner. Examiner is respectfully referred to MPEP 2164.04, which states: "it is incumbent upon the Patent Office, whenever a rejection on this basis [i.e. under the enablement requirement] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure *and to back up assertions of its own with acceptable evidence or reasoning* which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." MPEP 2164.04 (emphasis added) (quoting *In re Marzocchi*, 439 F.2d 220, 224).

Applicants note that the Examiner made several factual assertions in support of the contention that the claims were insufficiently enabled, to which Applicants responded by citing several publications as *evidence* contradicting the Examiner's assertions. Applicants note that although the Examiner readily attacks the evidence Applicants cited rebutting the reasons the Examiner gave for the rejection, the Examiner himself has yet to cite a single piece of evidence providing grounds to overcome the legal presumption of enablement.

Applicants also respectfully point out that the Examiner mischaracterizes Applicants' arguments in response to the prior enablement rejection. The evidentially-supported arguments for enablement presented by Applicants addressed specific (albeit evidentially-unsupported) arguments against enablement presented by the Examiner.

The Examiner questioned, for example, the enablement of compounds of claim 43 for the "broad use" for "inhibiting the proliferation of various cancer cells". The Examiner therefore questioned apparently whether it was credible that compounds could be effective against a broad range of cancers. Specifically the Examiner contended that it would be necessary that "each embodiment of the invention [would be] required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from the activity."

Applicants addressed this concern by presenting *evidence* that a common mechanism was involved in cancers (i.e. the cell cycle) and that compounds (such as cisplatin) that are known to be effective against cancer tend to be effective against a range of cancers. It is irrelevant to the point made that cisplatin is not structurally similar to the instant compounds. The point was that it would not be necessary to demonstrate utility against every disease individually to meet the enablement requirement since a common basic mechanism is known to be involved and established anticancer compounds have broad utility against numerous types of cancer.

Applicants also provided *evidence* that the in vitro models for which data were presented are established as being predictive of in vivo activity. Therefore, to satisfy the enablement, the in vitro data should be accepted as predictive of in vivo activity. As MPEP 2164.02 explains: "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate". Applicants have presented *evidence* that the in vitro models used by the Applicants are in fact predictive of in vivo activity. The Examiner has presented *no evidence* to the contrary. The Examiner should therefore accept the in vitro data presented by Applicants as being predictive of in vivo activity.

The Examiner's burden to present evidence in support of a rejection on the grounds of enablement is not relieved by mischaracterizing Applicants' remarks addressing the Examiner's evidentially-unsupported allegations as "admissions" of the truth of those allegations. Out of the utmost respect for the Examiner's views and the desire to address those concerns fully in response, Applicants may not always have expressed full disagreement, and may have appeared to assume the truth of certain statements in order to rebut the Examiner's arguments. Applicants herein expressly deny (and deny having admitted) that the treatment of cancer is an inherently unpredictable field. Applicants in fact presented evidence of a common mechanism involved in cancer, the known correlation of in vivo results to in vitro models, and the broad spectrum activity of several anti-cancer agents, all of which demonstrate substantial predictability of cancer treatment. Applicants' remarks on p. 58 of the response to the prior office action only acknowledged that response to treatment *in individuals* might be "somewhat unpredictable" due to factors "such as variability in the aggressiveness of the cancer, metastasis, and development of drug resistance." Such possible variability in individual response is irrelevant to consideration of compliance of whether the enablement requirement is satisfied.

Applicants also deny having admitted that the activity was not consistent across different diseases. Rather, Applicants stated on p. 60 of the prior response that "[t]he results showed remarkably consistent activity for any given compound across the different cell types". Applicants' comments in the following paragraph were that "to the extent that activity is not consistent across different diseases, the person skilled in the art who wished to use the invention to treat a particular disease could readily implement a suitable *in vitro* screen by selecting a suitable cell line". The statement is not an admission that activity was not consistent across different diseases, but merely points out that if activity were not consistent, no issue of lack of enablement would arise because the skilled artisan could readily screen compounds against a cell line selected to be particularly relevant to the disease sought to be treated.

The Examiner also appears to assert new reasons for the enablement rejection by suggesting that the generic claims are directed to a greater number of compounds than were specifically tested in the in vitro assays for which results were presented in Table 5. The

Examiner suggests that the data presented in Table 5 are not statistically representative of the scope of the claims, asking "[w]hat kid *(sic)* of statistical analysis can be drawn out of the test?". Applicants respectfully respond that the data in Table 5, while not representing every compound within the generic scope of the rejected claims, nevertheless include data for a reasonable range of representative compounds. Since the Applicants enjoy a legal presumption that the claims comply with 35 U.S.C. § 112, if the Examiner wishes to maintain a rejection under 35 U.S.C. § 112 alleging that the date presented in Table 5 are somehow not statistically representative of the claimed genus and cast doubt that Applicants have failed to describe to the skilled artisan how to make and use the claimed invention, then the burden is upon the Examiner to present the evidence in support of the rejection and not upon the Applicants to rebut a rejection which the Examiner has failed to support. Applicants fail to observe any evidence presented by the Examiner in support of the rejection, such as, for example, a statistical analysis demonstrating the inadequacy of the data presented in Table 5 to support the claimed utility.

Finally, the Examiner suggests that in view of Applicants' alleged admission that the state of the art is not absolutely predictable and alleged concession that it is possible that not every compound within the scope of the claimed invention will be useful, the Examiner suggest that the Applicants should limit the claimed scope of specific compounds that are effective against some cell lines. Applicants would not disagree that, if the Examiner had presented any evidentially-supported reasons that the claims of the instant invention should be narrowed for want of enablement, and Applicants had been unable to rebut such reasons, the claims should be narrowed to the scope enabled by the specification. However, in view of the fact that the Examiner has presented no evidence whatsoever rebutting the presumption of enablement, Applicants are of the view that any such narrowing of the rejected claims would be entirely unwarranted.

Since the Examiner has failed to present any evidence rebutting Applicants' presumption of enablement, withdrawal of the rejection under 35 U.S.C. § 112 is respectfully requested.

Should the Examiner present any evidence in support of the rejection under 35 U.S.C. § 112, such evidence having previously been completely lacking, the Examiner is respectfully requested to acknowledge that insofar as any such rejection relies on any such newly presented evidence, that such rejection would be recognized as new grounds of rejection such that the rejection would not be made final and Applicants would be afforded a first opportunity to rebut such grounds of rejection in response to the office action.

(3) Rejection of Claims 1-2, 22, 35, and 91 under 35 U.S.C. §103(a).

Claims 1-2, 22, 35, and 91 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Yamamori, *et al.*, JP 2001-139550 ("Yamamori"). Applicants respectfully traverse.

Applicants remain unclear as to whether the reference relied upon in making the rejection is the English-language abstract of Yamamori or the underlying full text reference (which is in the Japanese language). ***Applicants respectfully request that the Examiner expressly state whether the reference relied upon is the English-language abstract or the underlying full text reference in the Japanese language.*** If the Examiner wishes to rely on the Japanese-language full text publication, Applicants respectfully point out that the MPEP requires the Examiner to provide a translation of that document. MPEP 706.02. Applicants respectfully submit that if the Examiner is relying upon the Japanese-language full text document, any rejection made relying on that document could not properly be made final given that the MPEP requires that the Examiner provide a translation of a foreign language document relied upon in making a rejection.

The Examiner alleges that Yamamori "teaches structurally similar compounds." However, the broad genus of Yamamori is not so structurally similar to the claimed compounds that the reference would render Applicants' claims obvious. The Examiner consistently refuses to suggest a single species within the scope of the rejected claims that is taught or suggested by Yamamori, which speaks clearly to the point that the broad genus of Yamamori and the claimed

compounds are not so structurally similar. Beyond the assertion of "structural similarity" the Examiner fails to identify any reason why the skilled person would modify Yamamori to obtain compounds within the scope of each of the rejected claims.

In addition, on page 6 of the Office Action, the Examiner advises "that the reference should be read in its entirety as to what it teaches." As discussed above, this is an improper position since the entire reference is not in the English language.

Despite the lack of clarity, it is respectfully submitted that it is clear that the Examiner has not established a *prima facie* case of obviousness. A *prima facie* case of obviousness, in addition to showing the differences between the prior art reference and the claimed invention, must establish the reasons why the claimed invention would have been obvious, that is, why a skilled person would be led to modify the teachings of the reference to provide the claimed invention. MPEP 2141.III and 2142.

The English abstract of Yamamori demonstrates that an enormous diversity of compounds fall within formula I, which would not have obviously led to the instant claimed invention. It appears to be clear that the Examiner has used the Applicants' own teachings to make the appropriate selections in the generic formula set forth by Yamamori. However, the use of hindsight is not appropriate to establish why the presently claimed invention would have been obvious to the person skilled in the art at the time the presently climed invention was made. The MPEP makes clear that a *prima facie* case of obviousness must be established based on the reference itself unguided by the Applicants' disclosure, *i.e.* obviousness is determined looking forward from the reference, not backward from the claimed invention. Again, there is no teaching nor suggestion in Yamamori that would lead one of ordinary skill in the art to select the claimed compounds.

Looking to the untranslated Yamamori patent document itself, insofar as it is understood by Applicants, the Examiner has not stated a reason it would have been obvious to modify the compounds taught in the reference to make compounds within the scope of the rejected claims.

Applicants have set forth their assumptions concerning the content of the untranslated document in Applicants' response to office action mailed April 13, 2007, pp. 63-67. Notably, the essential features of the compounds of instant claim 1 appear infrequently in the compounds described in Yamamori, and do not appear together at all in any of the compounds of Yamamori.

In the present Office Action on page 6, the Examiner states: "Inasmuch the reference have made compounds having OH and OMe substituents, they are indeed equivalent." As this statement applies to the A ring of Yamamori, and since R^2 in current claim 1 has been amended to exclude OH, this issue appears to be moot.

Therefore, considering Yamamori as a whole, it is respectfully submitted that a person skilled in the art who wished to make more compounds with similar properties to those described by Yamamori would make compounds that had the features that are represented most frequently in the compounds that Yamamori made, as these would be assumed to be the features that impart the desired effectiveness to the compounds for treating arteriosclerosis. For example, it appears from Yamamori that for Ar^1, unsubstituted rings, particularly 2-pyridyl are strongly preferred, while for ring A, unsubstituted or monosubstituted rings are preferred. The person skilled in the art would therefore be led to make compounds with these features rather than features which would lead to compounds within the scope of the rejected claims. The data given on p. 38 of Yamamori (untranslated) reinforce this conclusion, showing that compound Ia-39 (having Ar^1=2-pyridyl and A=4-chlorophenyl) is the most potent compound for which data is presented.

Based on the foregoing, the Examiner has failed to establish a *prima facie* case of obviousness against claim 1 or the rejected claims depending therefrom. If the Examiner is relying on the Yamamori abstract only, the reasons why a skilled person would be led to select compounds within the scope of claim 1 from the multitude of structural possibilities represented by the abstract have not been clearly articulated. If the Examiner is relying on the underlying Yamamori publication, no translation has been provided, nor the reasons why a skilled person would be led to modify the reference. It is incumbent on the Examiner to provide reasons why

the skilled person would modify the Yamamori reference to provide the claimed invention in order to establish a *prima facie* case of obviousness.

I t is respectfully submitted that since the Examiner has failed to establish *prima facie* obviousness of claims 1-2, 22, 35, and 91, the rejection should be removed.

(4) Rejection of Claims 24-25 under 35 U.S.C. §103(a).

Claims 24-25 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,705,521 to Abraham, *et al.* ("Abraham"). Applicants respectfully traverse.

Applicants respectfully point out that the Examiner has failed to establish a *prima facie* case of obviousness. In claims 24-25, Applicants are claiming a method of making particular amides using particular starting materials. In order to establish a *prima facie* case of obviousness, the Examiner is required to clearly articulate the reasons why a skilled person would modify Abraham to perform the method steps of the rejected claims. Abraham does not teach or suggest the desirability of making such a modification. Furthermore, the Examiner has not given any other reason for making such a modification to Abraham, except that the processes disclosed in Abraham are "similar to those claimed," which is not a clear explanation. Applicants also point out that since R^2 in current claim 2 has been amended to exclude OH, the method shown in Figure 25 of Abraham, which requires OH on the phenyl group, cannot render the claims obvious.

In the Office Action on page 6, the Examiner indicates that if the compounds are patentable, the process of making the compounds is patentable. Applicants' understanding is that if the rejections of claims1-2, 22, 35, and 91 are removed, then claims 24-25 will be patentable. Based on Applicants arguments in section (3) and (4), therefore, the obviousness rejection of claims 24-25 should be removed.

Request for Rejoinder of Claims 26-34, 37, 42 and 53

Claim 37 and 42

Withdrawn claim 37 is directed to conjugates of compounds of claim 1. Withdrawn claim 42 is directed to a pharmaceutical composition of conjugates of claim 37. For the reasons set forth above, claim 1 is believed to be in condition for allowance.

Claim 37 depends from claim 1. Claim 42 depends from claim 37. Applicants therefore request rejoinder of claims 37 and 42 pursuant to MPEP 821.04(a). The latter mandates rejoinder of product claims that depend from or otherwise incorporate the limitations of other allowable product claims:

> Rejoinder Between Product Inventions; Rejoinder Between Process Inventions.
>
> When restriction was required between independent or distinct products, or between independent and distinct processes, and all claims directed to an elected invention are allowable, any restriction requirement between the elected invention and any nonelected invention that depends form or otherwise requires all the limitations of an allowable claim should be withdrawn.

Claims 26-34 and 53

Withdrawn claims 26-34 are directed to processes for making compounds according to claims 2, 16, 21, or 23. For the reasons set forth above, compound claims 2, 16, 21, and 23 are believed to be allowable.

Withdrawn claim 53 is directed to a method of use of a conjugate according to claim 37. For the reasons set forth above, conjugate claim 37 is believed to be allowable, and should be rejoined with claim 1 for examination. Consequently, withdrawn method claim 53, reciting a method of use of a conjugate according to claim 37, should also be rejoined for examination.

Claims 26-34 and 53 are directed to processes of making or using products that are defined in allowable product claims. Claims 26-34 and 53 depend from or otherwise require all the limitations of product claims that are believed to be allowable. Hence, Applicants request rejoinder of claims 26-34 and 53 pursuant MPEP 821.04(b). The latter mandates rejoinder of

process claims that depend from or otherwise incorporate the limitations of an allowable product claim:

> Rejoinder of Process Requiring an Allowable Product.
>
> Where claims directed to a product and to a process of making and/or using the product are presented in the same application, applicant may be called upon under 35 U.S.C. 121 to elect claims to either the product or a process. See MPEP § 806.05(f) and § 806.05(h). The claims to the nonelected invention will be withdrawn from further consideration under 37 CFR 1.142. See MPEP § 821 through § 821.03. However, if applicant elects a claim(s) directed to a product which is subsequently found allowable, withdrawn process claims which depend from or otherwise require all the limitations of an allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must depend from or otherwise require all the limitations of an allowable product claim for that process invention to be rejoined. Upon rejoinder of claims directed to a previously nonelected process invention, the restriction requirement between the elected product and rejoined process(es) will be withdrawn.

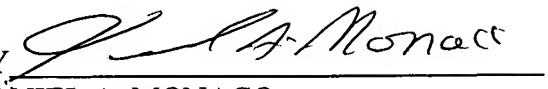
In conclusion, rejoinder of claims 26-34, 37, 42 and 53 is respectfully requested.

Applicants' comments in support of patentability of the rejected claims made in response to the office action would apply with full force to the claims as presently herein amended.

Applicants respectfully submit that upon entry of the presently submitted response, the application would be placed in condition for allowance. Applicants therefore respectfully solicit the entry of the submitted amendment and issuance of a notice of allowance.

Respectfully submitted,

M.V. Ramana REDDY, *et al.*

BY 

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